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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/871,491	05/31/2001	David H. Raulet	B01-088-1	8724

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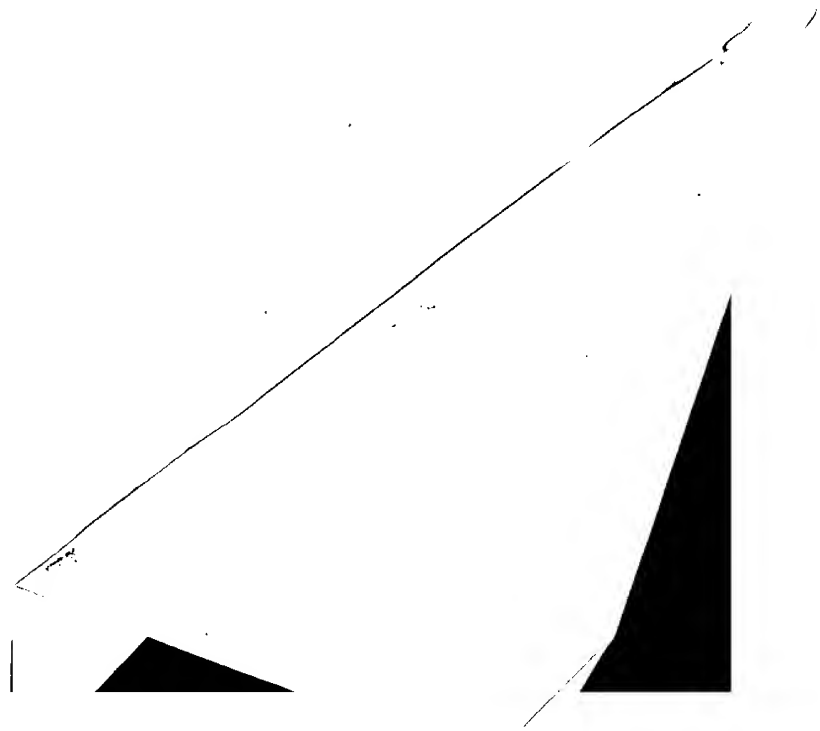
EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 12/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.



Office Action Summary	Application No.	Applicant(s)	
	09/871,491	RAULET ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the restriction of claims 1-18 into three separate groups in Paper No. 3, received October 7, 2002 is acknowledged. The traversal is on the ground(s) that "[t]he method steps are all the same in all the groups". The Examiner has found the arguments persuasive and as a result examined all claims.

2. Claims 1-18 are pending.

Claims 1-18 are examined on the merits.

Claim Objections

3. Claims 6 and 15 are objected to because of the following informalities: (a) claim 6 does not end with a period, hence it is not clear if any other text is missing and (b) in line 4 of claim 15 the term "biding" is misspelled. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' disclosure sets forth the use of three tumor types: EL4 (a thymoma), RMA (a T cell lymphoma) and B16-BL6 (a melanoma), see page 11, lines 18-22. All of these cell lines do not normally express NKG2D ligands and were transduced to ectopically express high levels of either Rae1β or H60 NKG2D ligands. These recombinant tumor cells were capable of binding NKG2D tetramers. Implanted Rae1β– or H60-transduced EL4 and B16-BL6 tumor cells were rejected rapidly and completely and failed to yield any detectable tumors in B6 mice, see bridging paragraph of pages 11 and 12. Additional evidence on page 11 provides support that rejection of Rae1β– or H60-transduced tumor cells is mediated by NK cells and that expression of either NKG2D ligand results in reduced frequency of lung metastases.

Applicants also provide evidence that suggest that prior immunization with transduced NKG2D ligand bearing tumor cells (EL4, B16-BL6 or RMA) induces protective immunity to ligand-negative tumor cells once rechallenged, see page 13, lines 9-16. However, none of the examples presented in Applicants' disclosure utilize NKG2D binding moieties consisting of MICA, MICB and ULBP ligands. Nor does Applicants' disclosure provide sufficient evidence that a composition comprising a multivalent NKG2D-binding agent can be administered with the imminent arrest of tumor growth. There is no data presented commensurate with the claims of administration a

multivalent NKG2D-binding agent consisting of several ligands resulting in the inhibition of tumor growth. Nor is there presentation of data that suggest that a multivalent NKG2D-binding agent consisting of one ligand is capable of binding several NKG2D receptors resulting in tumor inhibition. Neither one of these circumstances has been evidenced in the examples provided within the specification. There is inadequate direction or guidance provided to assist one skilled in the art in the selection of which types of cancers that fall under the scope of a tumor that could be treated with the composition comprising a multivalent NKG2D-binding agent with therapeutic effectiveness. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications. The specification does not teach how to extrapolate data obtained from observations set forth in the said examples to the implementation of administrating the said composition to any and all cancers. One cannot extrapolate the teachings of the specification to the plethora of disorders encompassed by the term cancer because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. For example, Gura (Science 278:1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (see first paragraph of page 1041).

Claims 1-18 are not enabled because there is insufficient evidence provided enabling one of ordinary skill in the art to determine susceptible cancer candidates within a population. The specification provides neither guidance on nor exemplification

of identifying a population of people who may eventually have a tumor. Furthermore, if such a group was identified there is insufficient evidence provided that the tumor growth would be inhibited with the administration of a multivalent NKG2D-binding agent.

In view of the analysis and teachings above, and the lack of guidance and or exemplify in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 18 are vague and indefinite in the recitation "determined to **harbor** a tumor" and "determined to...**harboring** a tumor". Specifically the term "harbor" and derivatives of the word are not art recognized in the context of a subject having a tumor. It is not clear how a tumor is harbored. Applicants are requested to use terminology reflective of the art.

b. Claims 1 and 18 are vague and indefinite in the recitation "multivalent NKG2D-binding agent". It is not clear if the binding agent binds two receptors or that there are several binding agents that bind one receptor. Accordingly, the metes and bounds cannot be determined.

c. Claims 1 and 18 are vague and indefinite in the recitation "detecting a resultant inhibition". The claims do not include how to determine tumor growth inhibition. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced.

e. Claims 2 and 3 are vague and indefinite in the recitations "detectable amount" and "undetectable amount". It is not clear what is regarded as a detectable or undetectable amount or how that is assessed. For instance is the amount detectable by the numerical amount of ligand or an optical result? As the claim is presently written the metes and bounds cannot be determined.

f. The phrase "tumor cells are substantially non-immunogenic" in claim 6 is vague and indefinite. Specifically the term "substantially" is not definitive. It is not clear if the cell for instance emits a response, releases cytokines at all, gradually or not significantly.

g. The recitation "highly" in claims 7 and 8 is vague and indefinite. It is not clear what parameters are encompassed by the said recitation in describing metastatic and tumorigenic.

8. Claims 1-18 are free of the art.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Diefenbach et al (Nature Immunology 1(2): 119-126, August 2000).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
December 16, 2002